



VERIFICATION

I, Kiyoshi TANAKA, a Japanese Patent Attorney registered No. 9058 having my Business Office at Yebisu Garden Terrace Nibankan 709, 20-2, Yebisu 4-chome, Shibuya-ku, Tokyo 150-0013 JAPAN, solemnly and sincerely verify, that I have a thorough knowledge of Japanese and English languages, that I am the translator, and that the attached papers contain a true and correct translation into English of the Japanese Patent Application No. 11-45696 filed on February 24, 1999.

Signed this 12th day of December, 2002


Kiyoshi TANAKA

PATENT OFFICE
JAPANESE GOVERNMENT

**This is to certify that the annexed is a true copy of
the following application as filed with this Office.**

Date of Application: February 24, 1999
Application Number: Patent App. 11-45696
**Applicant(s): Hisamitsu Pharmaceutical Co.,
Inc.**

Commissioner, Patent Office
(signature)

[Designation of Document] Patent Application

[Reference No.] HM990003

[Destination] Commissioner of the JPO

[IPC] A61N 1/30

[Inventor]

[Address or Domicile] c/o Tsukuba Laboratory of Hisamitsu
Pharmaceutical Co., Inc., 25-11, kannondai 1-chome, Tsukuba-shi,
Ibaraki

[Name] INOUE Kazutaka

[Inventor]

[Address or Domicile] c/o Tsukuba Laboratory of Hisamitsu
Pharmaceutical Co., Inc., 25-11, kannondai 1-chome, Tsukuba-shi,
Ibaraki

[Name] ADACHI Hirotoshi

[Inventor]

[Address or Domicile] c/o Tsukuba Laboratory of Hisamitsu
Pharmaceutical Co., Inc., 25-11, kannondai 1-chome, Tsukuba-shi,
Ibaraki

[Name] MAEDA Hiroyuki

[Inventor]

[Address or Domicile] c/o Tsukuba Laboratory of Hisamitsu
Pharmaceutical Co., Inc., 25-11, kannondai 1-chome, Tsukuba-shi,
Ibaraki

[Name] HIGO Naruhito

[Applicant]

[Identification No.] 000160522

[Name] HISAMITSU PHARMACEUTICAL CO., INC.

[Attorney]

[Identification No.] 100090583

[Patent Attorney]

[Name] TANAKA Kiyoshi

[Attorney]

[Identification No.] 100098110

[Patent Attorney]

[Name] MURAYAMA Midori

[Official Fee]

[Deposit Account No.] 051035

[Fee] ¥21,000

[List of Things Submitted]

[Designation of Thing]	Specification	1
------------------------	---------------	---

[Designation of Thing]	Drawing	1
------------------------	---------	---

[Designation of Thing]	Abstract	1
------------------------	----------	---

[Request for Proof] Yes

[Designation of Document] Specification

[Title of the Invention] Device for iontophoresis

[Claims]

[Claim 1] A device for iontophoresis supplying a drug to
5 transdermal or transmucosal, comprising: first means for detecting
a capacitance stored in the transdermal or the transmucosal; and
second means for determining a conduction state of current into
the transdermal or the transmucosal based on the output detected
by the first means.

10 [Claim 2] The device for iontophoresis according to Claim 1,
wherein the first means is a detection circuit for a reactive current
flowing through the transdermal or the transmucosal.

[Claim 3] The device for iontophoresis according to Claim 1,
wherein the first means is a detection circuit for a residual voltage
15 developed in the transdermal or the transmucosal.

[Claim 4] A method for determining an operation of an
iontophoresis apparatus, wherein a capacitance stored in
transdermal or transmucosal is detected to determine a conduction
state of current flowing into the transdermal or the transmucosal.

20 [Claim 5] The method for detecting an operation of an
iontophoresis apparatus according to Claim 4, wherein the detection
of the capacitance is carried out by detecting a reactive current
flowing through the transdermal or the transmucosal.

[Claim 6] The method for detecting an operation of an
25 iontophoresis apparatus according to Claim 4, wherein the detection
of the capacitance is carried out by detecting a residual voltage
developed in the transdermal or the transmucosal.

[Claim 7] An iontophoresis apparatus comprising: a
preparation for iontophoresis, holding a drug; and a device for

iontophoresis having means for generating an electrical output to supply a drug from the preparation into transdermal or transmcosal and means for detecting a capacitance stored in the transdermal or the transmcosal to determine a conduction state
5 of a current flowing into the transdermal or the transmcosal.

[Detailed Description of the Invention]

[0001]

[Technical Field of the Invention]

The present invention relates to a device for use in an
10 iontophoresis apparatus that is applied to transdermal or transmcosal.

[0002]

[Prior Art]

Iontophoresis is a percutaneous absorption promoting system
15 using electricity, which is based on the principle that forces act on charged molecules such that positively charged molecules transfer from a positive electrode to a negative electrode and negatively charged molecules migrate from the negative electrode to the positive electrode in an electric field generated by passing
20 of electric current, thereby accelerating drug delivery through skin barrier. (Refer to "Journal of Controlled Release", Vol. 18, 1992, pp. 213-220; "Advanced Drug Delivery Review", Vol. 9, 1992, p. 119; and "Pharmaceutical Research", Vol. 3, 1986, pp. 318-326.)

25 [0003]

There are conventional means for checking whether the transfer of molecules (including drug) is normally carried out. For example, an iontophoresis apparatus from Motion Control, Inc. determines a value of an output current to that of an output voltage when

a direct current is applied to a subject. If the value of the output current is less than a certain value, then it is determined that the transfer of molecules is abnormal, and the application of output voltage is interrupted. However, in this method, a load of a human body at the initial stage of energization may be as high as several M Ω to several tens M Ω at low output voltages and it is difficult to determine whether there is conduction or non-conduction of current. Therefore, a relatively high voltage is applied initially to determine whether there is conduction or non-conduction.

[0004]

International Publication No. WO96/17651 discloses an apparatus in which the transdermal is first hydrated for a certain length of time before electrically energizing a human body, then the output current is measured and the output voltage is interrupted if the measured output current is out of a certain range. International Publication No. WO88/08729 discloses another related technique, i.e., an apparatus in which when an over-current flows, the supply of output current is terminated.

[0005]

[Problem to be solved by the Invention]

With these apparatus, there are problems about the DC impedance used as a measure means of conduction such that differences in individual are large and that the impedance is high and even higher at lower output voltages and that the impedance is highly sensitive to the hydration conditions. Therefore, conventionally, conduction in iontophoresis cannot be determined with a sufficient level of accuracy.

[0006]

In order to overcome the aforementioned problems, although it is considered in such a way that a relatively high voltage at the initial stage of energization may be applied or sufficient hydration of the transdermal may be employed to increase detection sensitivity of impedance, it produces new problems that users may feel uncomfortable or that the states of current conduction cannot be measured until the hydration is sufficient.

[0007]

An object of the present invention is to overcome the aforementioned problems and to provide a device for iontophoresis that can determine conduction states with a high level of accuracy.

[0008]

[Means of solving the Problem]

The inventors have concentrated in order to achieve the aforementioned object. The inventors focussed on the capacitance that exists in the transdermal or the transmcosal, and they found that detecting the current (reactive current) that flows through the capacitance or the charges (residual voltage) stored in the capacitance allows determining of the conduction states, and then made the present invention accordingly. The present invention allows determining of not only conduction states due to complete detachment of a part for applying iontophoresis to the transdermal or poor contact at a terminal or cracks in the electrode, but also the conditions of the transdermal to which iontophoresis is applied.

[0009]

A device for iontophoresis according to the present invention comprises first means for detecting a capacitance stored in transdermal or transmcosal and second means for determining a conduction state of current into the transdermal or the transmcosal

based on the output detected by the first means. The first means can be, for example, a detection circuit for a reactive current flowing through the transdermal or the transmcosal or a detection circuit for a residual voltage developed in the transdermal or the transmcosal. If the detection circuit of the reactive current is used, the voltage applied to the subject has a waveform such as an AC wave, a rectangular wave, or a DC wave on which a rectangular wave is superimposed, or a DC wave on which an AC wave is superimposed. If the detection circuit of residual voltage is used, the voltage applied is an intermittent waveform.

[0010]

With a method for determining the operation of an iontophoresis apparatus according to the present invention, a capacitance in the transdermal or the transmcosal is detected to determine the operation of a conduction state of current through the transdermal or the transmcosal. The capacitance is detected by detecting a reactive current that flows through the transdermal or the transmcosal, or detecting a residual voltage developed in the transdermal or the transmcosal.

[0011]

An iontophoresis apparatus according to the present invention comprises a preparation for iontophoresis, holding a drug, and a device for iontophoresis having means for generating an electrical output to supply a drug from the preparation into the transdermal or the transmcosal and means for detecting a value indicative of a capacitance of the transdermal or the transmcosal to determine whether conduction of electrical output into the transdermal or transmcosal is normal or abnormal.

The aforementioned configuration makes it possible to

accurately determine the conduction state for an iontophoresis apparatus.

[0012]

[Embodiments of the Invention]

5 FIG. 1 is a general cross-sectional view illustrating an example of an iontophoresis apparatus according to the present invention. As shown in the figure, the apparatus comprises a preparation 80 for iontophoresis, which holds a drug or drugs and a device 90 for iontophoresis, which serves as a power supply for
10 generating an electrical output that supplies the drug from the preparation to the transdermal or the transmucosal. The preparation 80 comprises an insulation substrate 1, a drug reservoir side electrode 2, an electrolyte reservoir side electrode 3, a drug reservoir 4, an electrolyte reservoir 5, and tabs 6A and 6B for
15 detachably attaching a device 90 to the preparation 80. The tabs 6A and 6B are connected to the electrodes 2 and 3, respectively. The device 90, as mentioned below, includes a circuit that detects a value reflecting a capacitance of the transdermal or the transmucosal to determine whether the electrical output flows
20 normally through the transdermal or the transmucosal.

[0013]

 An iontophoresis apparatus according to the present invention can be of any type that can be used in a conventional manner. In other words, the apparatus comprises a power supply, electrodes,
25 at least one drug reservoir, and at least one electrolyte reservoir. (If there are two or more drug reservoirs, the electrolyte-holding reservoir is not essential). The drug reservoir and electrolyte reservoir may be attached to, for example, the skin or the transmucosal directly or indirectly.

[0014]

When the iontophoresis apparatus is operated, charges are stored in the transdermal or the transmcosal. This is referred to as a capacitance of the transdermal or the transmcosal. For example, when the drug reservoir and electrolyte reservoir are not in intimate contact with the transdermal etc., the capacitance of the transdermal etc. causes a decrease in reactive current and a decrease in charge (an element determining a time constant of the residual voltage) stored in the skin. When this happens, for an output voltage, it causes that the reactive current does not reach a predetermined value or the residual voltage does not reach a predetermined value. Thus, detecting the the reactive current or residual voltage allows accurate, quick determining of current a conduction state of the iontophoresis apparatus, thereby being able to prevent an abnormal condition.

[0015]

When abnormal conditions occur such as damage to the skin, short-circuit due to poor printing of conductive paste during the manufacture of the drug reservoir side electrode and the electrolyte reservoir side electrode, or short-circuit etc. due to perspiration etc., the DC impedance prominently drops so that the DC current exceeds a predetermined value. Thus, these abnormal conditions can be determined by detecting a DC impedance as in the conventional art.

25 [0016]

The impedance of the capacitance (described below as capacity) of the transdermal and the transmcosal, for example, described in "IYODENSHI TO SEITAIKOGAKU" Vol. 11, No. 5, pp337-343. According to this document, using an electrode about 9 mm (0.64

cm²), subjecting the transdermal to hydration for more than 30 minutes, and supplying a current for a predetermined length of time, then, the result of the measurement is that the impedance of the transdermal is about 1.8 k Ω on an AC signal of 10 kHz (calculated as R_p: 4 k Ω and C_p: 0.008 μ F) and is about 0.36 k Ω on an AC signal of 100 kHz (calculated by assuming that R_p = 0.4 k Ω and C_p = 0.002 μ F). R_p, here, is a resistance component of an equivalent circuit of the skin impedance and C_p is a capacity component. Detection of the reactive current is to measure a current that flows through the impedance of the capacity for AC current.

[0017]

While the time constant of a living organism for DC current is about 6 ms (calculated as R_p: 100 k Ω and C_p: 0.06 μ F), when no load is connected to the apparatus, there is no capacity and therefore a time constant seen from the apparatus is uncertain. Thus, a discharging resistor of, for example, 100 k Ω to 1M Ω is used in the circuit to provide a time constant of 0 ms. Detection of residual voltage is to measure the difference in time constant between them.

[0018]

When the device for iontophoresis uses a waveform such as an AC waveform, a rectangular waveform, a DC waveform to which a rectangular waveform is superimposed, or a DC waveform to which an AC waveform is superimposed, a current is stored into the capacity of the skin during the positive period of the time-varying component and discharged from the capacity during the negative period. A reactive current that flows through the skin is detected by thus repeatedly storing and discharging the current.

[0019]

When an intermittent current is used, a charge (voltage) is stored in the capacity of the skin by conducting the output, and the charge remains in the capacity during the off-period of the output and causes a voltage so that a residual voltage is measured.

In order to know the conduction states for the iontophoresis apparatus, it is sufficient to measure either the reactive current or the residual voltage.

Moreover, a display function such as a light emitting diode (LED) or a buzzer and a function for adjusting or interrupting the output may be added to the device for iontophoresis according to the present invention, in order to indicate to the user when an abnormal condition is determined by detecting the reactive current or residual voltage.

[0020]

FIG. 3 illustrates an example of a detecting circuit for output current to detect a reactive current resulting from the capacity of the skin. In this embodiment, the output waveform superimposed with frequency components is used. Referring to FIG. 3, reference numerals 7B and 8B denote a negative output terminal and a current-detecting fixed resistor, respectively. Reference numerals 9B, 10B, and 11B denote a circuit ground, a voltage comparator, and an output signal from the voltage comparator, respectively. Reference numerals 12, 13, and 14 denote a current-storing capacitor, a discharging fixed resistor, and an analog switch, respectively.

FIGS. 4(a)-(d) illustrate voltage waveforms or current waveforms, respectively. When the output is a rectangular waveform having a frequency of 10 kHz and a duty cycle of 50% as shown

in FIG. 4(a), the current outputted from the negative output terminal 7B is converted into an output current waveform 16 as shown in FIG. 4(b) by the fixed resistor 8B. By an analog switch 14 in synchronism with the output, the output current waveform 16 is passed as only the positive current waveform 17 as shown in FIG. 4(c) to a capacitor 12 of the succeeding stage, and then an output current signal 18 as shown in FIG. 4(d) is produced by smoothing out the waveform.

[0021]

10 The voltage comparator 10B compares the output current signal 18 indicative of the reactive current that flows through the skin or the mucous with a threshold level SL pre-adjusted to a voltage value corresponding to a lower limit of the reactive current, thereby determining whether a reactive current exists. When the
15 output current signal 18 is higher than the threshold level SL, the voltage comparator 10B outputs an output signal 11B of "H" to indicate to a control circuit that a conduction state is normal. When the output current signal 18 is lower than the threshold level SL, the voltage comparator 10B outputs the output signal 11B of
20 "L" to indicate to the control circuit that a conduction state is abnormal.

[0022]

 The threshold level can be set to a voltage value that corresponds to a reactive current in the range of 0.01 to 10 mA
25 and more preferably 0.1 to 1 mA, so that the conduction state may be detected even at low voltages. In order to detect poor intimate contact, a D/A converter can be used to adjust the threshold level in accordance with the area of the preparation applied to the subject and the output voltage. Also, an A/D converter is used in place

of the voltage comparator 10B to change detection conditions in accordance with the output voltage etc. Additionally, a voltage amplifier for amplifying the output signal 18 may be added to the forward stage etc. of the voltage comparator 10B, or a feedback
5 signal of the output voltage may be used as the threshold level, so that the threshold level has a voltage value proportional to the output voltage.

For the detection of a reactive current, a sample-and-hold circuit may conveniently be used to detect positive portions of
10 the reactive current. Instead of detecting only the reactive current, the current including a current for conveying the drug may be detected, or a part of the reactive current may be detected. Further, a function for detecting a part of the DC current may be provided.

15 [0023]

FIG. 5 illustrates an example of a detecting circuit for residual voltage to detect the residual voltage developed across the skin (load). In the present embodiment, an intermittent energization is used. Referring to FIG. 5, reference numerals
20 19, 20, and 21 denote an output circuit, an analog switch, and an output terminal A, respectively. Reference numerals 22, 23, and 24 denote an output terminal B, a discharging fixed resistor, an output signal to the voltage comparator, respectively. Reference numerals 25, 26 and 27, and 28 denote a voltage comparator,
25 voltage adjusting fixed resistors, and an output signal from the voltage comparator, respectively.

FIG. 6 illustrates voltage waveforms across the output terminals. Referring to FIG. 6, a voltage waveform 29 describes the output signal across the output terminals when a load is

connected across the output terminals and a voltage waveform 30 represents the output signal across the output terminals when no load is connected across the output terminals.

[0024]

5 The DC output voltage from the output circuit 19 is usually outputted to the output terminal 21 through the analog switch 20. When the residual voltage is detected, the analog switch 20 is a non-conduction state by a signal issued from the control circuit. Then, the voltage comparator 25 compares the output signal 24 when
10 the output voltage sent to the output terminal 21 is interrupted, with the threshold level that is produced by dividing the output voltage from the output circuit 19 by the fixed resistors 26 and 27. If the output signal 24 indicative of the residual voltage stored in the skin or the mucous is higher than the threshold level,
15 the voltage comparator 25 generates an output signal 28 of "H", indicating to the control circuit that the conduction state is normal. Conversely, if the output signal 24 is lower than the threshold level, the voltage comparator 25 generates the output signal 28 of "L", indicating to the control circuit that the
20 conduction state is abnormal.

[0025]

 The fixed resistor 23 is provided to prevent the output terminal 21 from being open-circuited when the analog switch 20 is the non-conduction state and there is no loading, and to allow the
25 residual voltage on the output terminal 21 to discharge with an arbitrary time constant when the analog switch 20 is the non-conduction state and there is a loading. The output signal 24 may be obtained by dividing a voltage on the output terminal 21 or a signal with a level lowered to a voltage level for the

control circuit, and then which may be provided in a variety of ways. Likewise, the threshold level may be modified in a variety of ways just as in the detection of the reactive current.

[0026]

5 The residual voltage is measured or detected in synchronism with the interruption of the output voltage and therefore the measurement or detection of the residual voltage can be performed in several microseconds to several seconds without affecting the output. Just as in the measurement of the reactive current,
10 adjusting the time constant and digitizing the voltage with an A/D converter, or adjusting the time between the interruption and reading-in allows determining of whether the preparation is in intimate contact with the transdermal or the transmcosal.

[0027]

15 The output waveform used for detecting the reactive current in the present invention contains a DC component for drug dosage and a frequency component for detection of a capacitive impedance. Means for detecting the impedance may be one that integrates or peak-holds the current resulting from repetitive application of
20 pulses, or one that performs the detection in real time with one shot of pulse triggered. If detection of impedance at all times is not required, then a frequency component may be superimposed to the output signal at an arbitrary timing to detect the impedance of the capacity. The waveform of an intermittent output signal
25 used in detecting the residual voltage may be one in which a DC current is interrupted at an arbitrary time intervals and the residual voltage remaining on the load is measured immediately after the output is interrupted. Thus, observing the voltage remaining on the load allows detection of impedance of the capacity.

[0028]

FIG. 7 illustrates a device for iontophoresis having a circuit for detecting the reactive current shown in FIG. 3. Referring to FIG. 7, reference numerals 31 and 32 denote a battery and a fixed resistor that limits the current flowing through a light-emitting diode (LED), respectively. Reference numerals 33, 34, and 35 denote an LED, a power switch, and a buzzer, respectively. Reference numerals 36, 37, and 38 denote microcomputer, a D/A converter, and a boosting coil, respectively. Reference numerals 39, 40, and 41 denote a coil-driving transistor, a rectifying diode, and rectifying capacitor, respectively. Reference numerals 42, 43, 44, and 48 denote fixed resistors that limit current. Reference numerals 45, 46, 47 denote output transistors. Reference numerals 49, 50, 51, 52, and 53 denote a current detecting fixed resistor, an analog switch, a current storing capacitor, a discharge fixed resistor, and a voltage comparator, respectively.

[0029]

The essential operation of the device according to the invention will now be described with reference to the figures. When the power switch 34 is pressed, the microcomputer 36 is activated to start to give a drug to a subject under a specific procedure previously programmed. The microcomputer 36 causes the LED 33 to light up and then causes the transistor 39 to oscillate to boost the voltage of the battery 31. When the transistor 39 oscillates, a back electromotive force is developed across the coil 38 and charges the capacitor 41 through the diode 40. The microcomputer 36 controls the transistors 45, 46 and 47, which are repeatedly conducted and non-conducted in opposite phase, and

therefore the voltage across the capacitor 41 is outputted in the form of a rectangular wave having a certain frequency to the output terminal A. If a load has been connected across the output terminals A and B, a current in accordance with the impedance of the load flows through the output terminal B, causing a current waveform to appear across the fixed resistor 49 in accordance with the amount of current. The analog switch 50 operates to sample-and-hold only the positive waveform of the current. The sampled positive waveform is smoothed out by the capacitor 51 and is then outputted to the positive input of the voltage comparator 53. The negative input of the voltage comparator 53 receives the threshold level corresponding to a lower limit of the reactive current, which is the output signal of the microcomputer 36 having been digital-to-analog converted by the D/A converter 37.

15 [0030]

The voltage comparator 53 compares these two inputs and provides the comparison result to the microcomputer 36. If the output signal of the voltage comparator 53 is "H", the microcomputer 36 determines that conduction is normal. If the output signal of the voltage comparator 53 is "L", the microcomputer 36 determines that conduction is abnormal. When the conduction is abnormal, the LED 33 flashes and the buzzer 35 sounds to warn the operator. If the abnormal conduction state is not remedied a certain length of time after the warning, the output is interrupted and the operator is informed that the output has been interrupted, the buzzer 35 continuing to sound and the LED 33 being de-energized. Performing these operations in sequence secures the safety of the user.

[0031]

FIG. 8 illustrates an iontophoresis device having a circuit

fordetectingaresidualvoltage,usingamicrocomputer. Referring
to FIG. 8, reference numerals 54, 55, and 56 denote a battery,
a fixed resistor that limits the current flowing through an LED,
and an LED, respectively. Reference numerals 57, 58, and 59 denote
5 a power switch, a buzzer, and a microcomputer that incorporates
an A/D converter, respectively. Reference numerals 60, 61, and
62 denote a boosting coil, a transistor for driving the coil, and
a rectifying diode, respectively. Reference numerals 63, 64-66,
and 67-68 denote a rectifying capacitor, fixed resistors that limit
10 current, and output transistors, respectively. Reference
numerals 69-70, 71, and 72 denote discharging fixed resistors for
detecting the residual voltage, fixed resistors for detecting the
current, a fixed resistor for limiting current, respectively.
Reference numerals 73, 74-75, and 76 denote a current-storing
15 capacitor, a fixed resistor for adjusting an amplification factor,
and a voltage amplifier, respectively.

[0032]

The basic operations of the device according to the present
invention will now be described with reference to the figures.
20 When the power switch 57 is pressed, the microcomputer 59 is
activated to start to give a drug to a subject under a procedure
previously programmed. The microcomputer 59 causes the LED 56
to light up and then causes the transistor 61 to oscillate, thereby
producing a voltage that is boosted from the voltage of the battery
25 54. When the transistor 61 oscillates, a back electromotive force
is developed across the coil 60, the back electromotive force being
stored in th capacitor 63 through the diode 62. When the
microcomputer 59 controls the transistor 67 to conduct the
transistor 68, the voltage held across the capacitor 63 is directed

to the output terminal A.

[0033]

When the transistor 68 is then turned off, a residual voltage appears on the output terminal A if a load has been connected to the output terminals. The residual voltage is divided by fixed resistors 69 and 70 and is then directed to the analog input terminal of the A/D converter in the microcomputer 59. When the measured voltage has reached a predetermined value, the microcomputer 59 determines that the conduction state is normal. When the measured voltage has not reached the predetermined value, the microcomputer 59 determines that the conduction state is abnormal. If the conduction state is abnormal, then the microcomputer 59 causes the LED 56 to flash and the buzzer 58 to sound, thereby warning the operator. If the abnormal condition is not solved beyond a certain period of time, then the microcomputer 59 shuts off the output. Then, the microcomputer 59 causes the buzzer to sound and the LED to go off, thereby indicating to the user that the output has been interrupted. Performing these operations in sequence secures the safety of the user.

[0034]

If a constant current means, which comprises circuit elements 71-76 to keep the current (current for giving a drug) flowing through the DC impedance to a predetermined value, is used as the output controlling means, an excess current is to be prevented from flowing through the load so that safety is improved. When the preparation comes off or floats from the applied part of the human body, a general iontophoresis apparatus may not only fail to give a sufficient amount of drug to the applied part but also cause concentration of current in areas still in intimate contact with

it. This may result in excessive supply of drug in particular small areas and electric burn. In contrast to this, the iontophoresis apparatus according to the present invention electrically energizes the body while making sure that a reliable electrical path is established for giving a drug. If an abnormal impedance should be detected, the apparatus warns the user, requesting of an improvement or interrupting the output, if necessary, to ensure safety of the user.

[0035]

10 Examples

(Example 1)

A device for iontophoresis incorporates a detecting circuit for an output current as shown in FIG. 3, which used a rectangular wave having a frequency of 10 kHz and a duty cycle of 50% as an output voltage that was variable from 0 V to 10 V in increments of 2 V. The detection conditions were as follows. The current-detecting fixed resistor 8B was 1 k Ω . The current-storing capacitor 12 was 0.1 μ F. The discharging fixed resistor 13 was 1 M Ω . The threshold level of the voltage comparator 10B was adjusted to 0.1 V. When the iontophoresis apparatus incorporating the aforementioned iontophoresis device was used, each of the positive and negative electrodes applied to the skin had an area of 5 cm².

[0036]

25 (Example 2)

A structure of the device for iontophoresis of Example 2 is the same as that of Example 1, which used a rectangular wave having a frequency of 10 kHz and a duty cycle of 50 % as the output voltage that was adjusted to a 5V. The detection conditions were as follows.

The current-detecting fixed resistor 8B was 1 k Ω . The current-storing capacitor 12 was 0.1 μ F. The discharge fixed resistor 13 was 1 M Ω . The threshold level of the voltage comparator 10B was adjusted to 0.5 V, which was 1/10 of the output voltage.

- 5 When the iontophoresis apparatus incorporating the aforementioned iontophoresis device was used, each of the positive and negative electrodes applied to the skin had an area of 5 cm².

[0037]

(Example 3)

- 10 A device for iontophoresis incorporates a detecting circuit for a residual voltage as shown in FIG. 5, in which the output voltage of the output circuit 19 was adjusted to a DC voltage of 5 V, and the analog switch 20 was closed to direct 5 V to the output terminal 21 and then the analog switch 20 was opened. The detection
15 conditions were as follows. The voltage-adjusting fixed resistor 26 was 10 k Ω . The voltage-adjusting fixed resistor 27 was 90 k Ω . The threshold level of the voltage comparator 25 was 4.5 V, which was 9/10 of the output voltage. When the iontophoresis apparatus incorporating the aforementioned iontophoresis device was used,
20 each of the positive and negative electrodes applied to skin had an area of 5 cm².

[0038]

(Comparison 1)

- 25 A device for iontophoresis incorporates a detecting circuit for an output current as shown in FIG. 2. The detecting circuit for the output current comprises a negative-electrode side output terminal 7A, a current-detecting fixed resistor 8A, a circuit ground 9A, and a voltage comparator 10A as shown in FIG. 2, obtaining an output signal 11A from the voltage comparator 10A. In this

embodiment, a DC voltage was used as the output voltage that was variable from 0 V to 10 V in increments of 2V. The detection conditions were as follows. The current-detecting fixed resistor 8A was 1 k Ω and the threshold level of the voltage comparator 10A was 0.1 V. When the iontophoresis apparatus incorporating the
5 aforementioned iontophoresis device was used, each of the positive and negative electrodes applied to the skin had an area of 5 cm².

[0039]

(Test 1)

10 For Example 1 and Comparison 1, Table 1 lists the input voltages to the voltage comparators 10A and 10B and the output signals 11A and 11B with different values of the output voltage.

[0040]

[Table 1]

Output voltage (V)	Example 1		Comparison 1	
	Input voltage (V)	Detection of conduction	Input voltage (V)	Detection of conduction
0	0	×	0	×
2	0.19	○	0	×
4	0.43	○	0	×
6	0.69	○	0	×
8	0.97	○	0.03	×
10	1.24	○	0.12	○

15 [0041]

If the output signal (detection of conduction) is "H" (indicated by ○), then it is determined that conduction is normal. If the output signal is "L" (indicated by ×), then it is determined that conduction is abnormal. As shown in Table 1, in Example 1,
20 conduction was observed at an output voltage equal to or higher than 2 V. In contrast to this, in Comparison 1, conduction was observed only at an output voltage of 10 V. This indicates that

the circuit according to Example 1 has higher detection accuracy than Comparison 1.

[0042]

(Test 2)

5 In Example 2, a detachment test was conducted with 3 subjects to determine whether the device was detached from the applied part of the transdermal. The result is as follows.

[0043]

[Table 2]

Area of the applied part	Subject 1		Subject 2		Subject 3	
	Voltage (V)	Detection of detachment	Voltage (V)	Detection of detachment	Voltage (V)	Detection of detachment
0/10	0	L	0	L	0	L
2/10	0.17	L	0.17	L	0.18	L
4/10	0.29	L	0.30	L	0.31	L
6/10	0.39	L	0.40	L	0.41	L
8/10	0.47	L	0.48	L	0.48	L
10/10	0.53	H	0.55	H	0.56	H

10 [0044]

The test was conducted in such a way that the output voltage was 5 V, and the device was peeled off the transdermal slowly so that the area of the device in contact with the applied part of the transdermal varies from 0/10 to 10/10. For different sizes
15 of the applied area, the input voltage and output signal 11B (detection of detachment) of the voltage comparator 10B were measured. "L" of the output signal 11B indicates that conduction was abnormal and "H" indicates that conduction was normal. From Table 2, the iontophoresis device according to Example 2 can detect
20 detachment of the device encountered, even a small area, during the application.

[0045]

(Example 3)

In Example 3, a detachment test was conducted in the same manner as Example 2. The result is as follows.

[0046]

[Table 3]

Area of the applied part	Subject 1		Subject 2		Subject 3	
	Voltage (V)	Detection of detachment	Voltage (V)	Detection of detachment	Voltage (V)	Detection of detachment
0/10	0	L	0	L	0	L
2/10	1.6	L	1.6	L	1.5	L
4/10	2.7	L	2.6	L	2.6	L
6/10	3.7	L	3.6	L	3.5	L
8/10	4.2	L	4.2	L	4.1	L
10/10	4.8	H	4.8	H	4.7	H

5 [0047]

The test was conducted in such a way that the output voltage was 5 V, and one of the areas of the device in contact with the applied part of the transdermal was varied from 0/10 to 10/10. The voltage on the output terminal 21 and the output signal 28 were measured 1 ms after the analog switch 20 was opened. "L" of the output signal 28 (detection of detachment) indicates that conduction was abnormal and "H" represents that conduction was normal. From Table 3, the iontophoresis device according to Example 3 can detect detachment of the device encountered, even a small area, during the application.

[0048]

[Effect of the Invention]

According to the present invention, a device for iontophoresis that can determine conduction states with a high level of accuracy, can be provided.

[Brief Description of the Drawings]

[FIG. 1]

This is a general cross-sectional view illustrating an example

of an iontophoresis apparatus according to the present invention.

[FIG. 2]

This illustrates an example of an output current detecting circuit.

5 [FIG. 3]

This illustrates an example of an output current detecting circuit.

[FIG. 4]

(a)-(d) illustrate voltage waveforms or current waveforms
10 on various parts, respectively.

[FIG. 5]

This illustrates an example of a residual voltage detecting circuit.

[FIG. 6]

15 This illustrates a voltage waveform across the output terminals of the residual voltage detecting circuit.

[FIG. 7]

This illustrates a device for iontophoresis that incorporates a reactive current detecting circuit.

20 [FIG. 8]

This illustrates a device for iontophoresis that incorporates a residual voltage detecting circuit.

[Explanation of the Symbols]

7B negative side output terminal

25 8B current-detecting fixed resistor

9B circuit ground

10B voltage comparator

11B output signal

12 current-storing capacitor

13 discharging fixed resistor

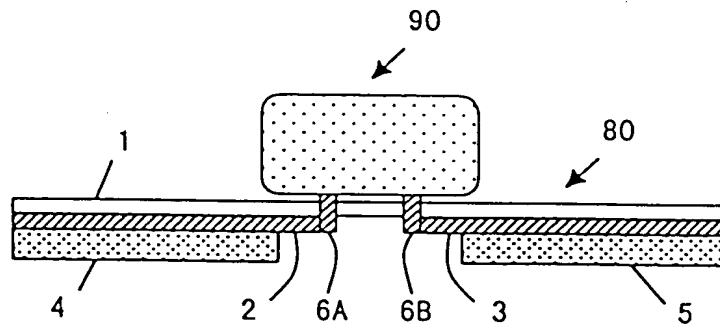
14 analog switch

18 output current signal

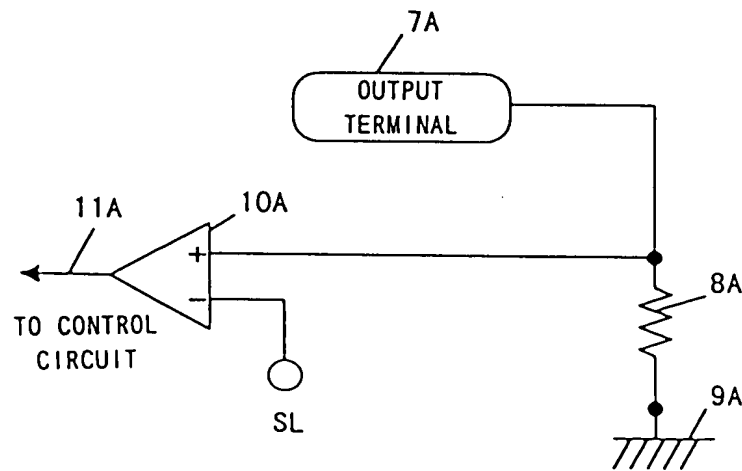
SL threshold level

[Designation of Document] Drawing

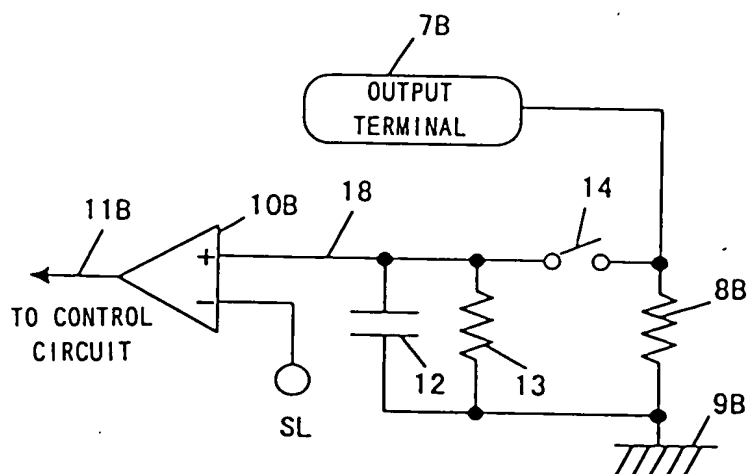
[Fig.1]



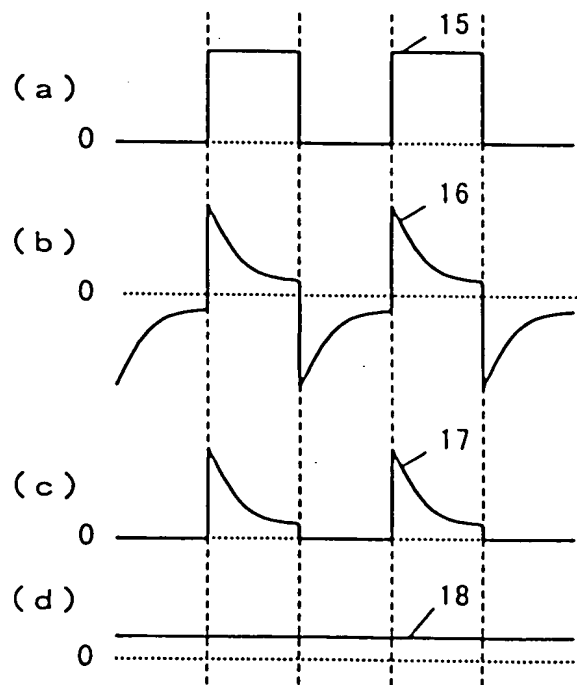
[Fig.2]



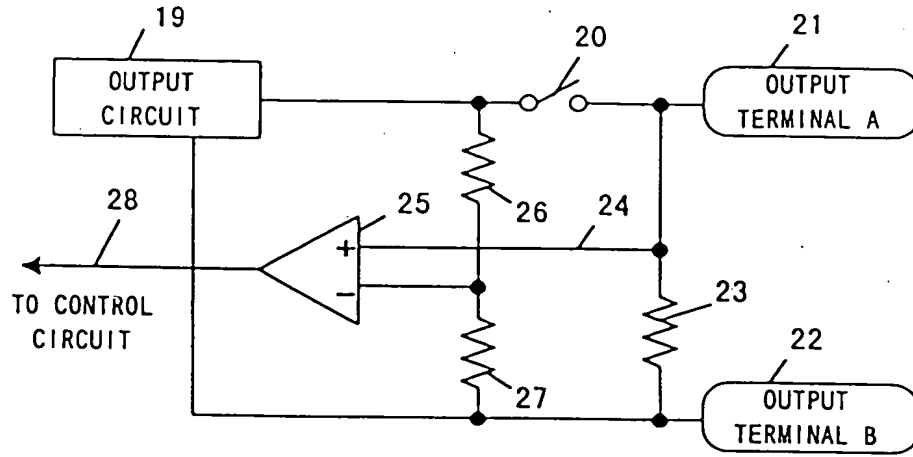
[Fig.3]



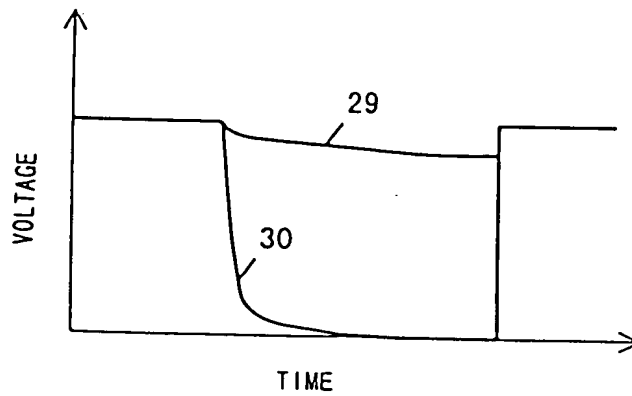
[Fig.4]



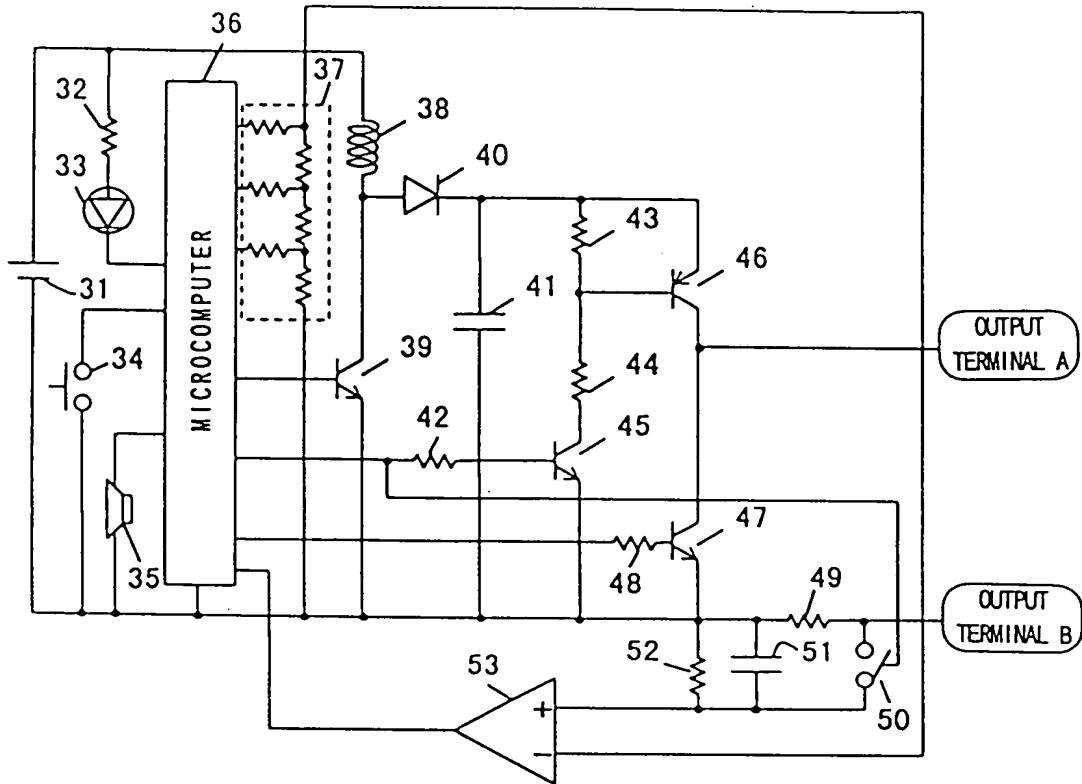
[Fig.5]



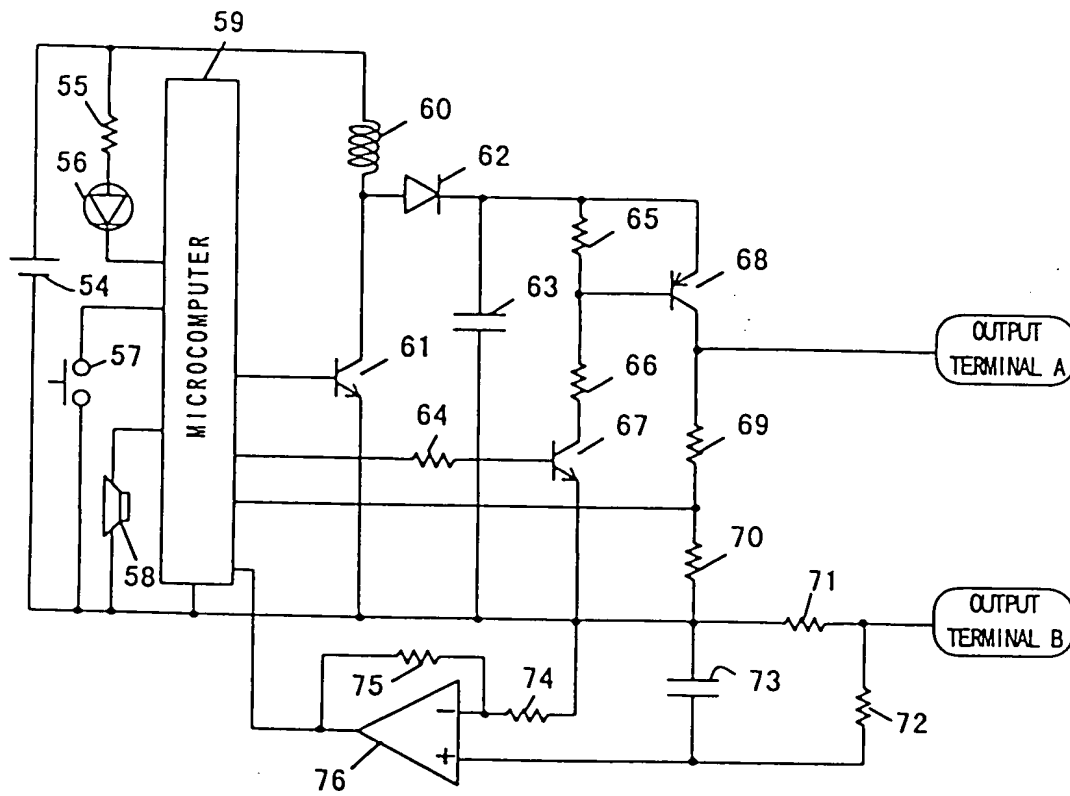
[Fig.6]



[Fig. 7]



[Fig.8]



[Designation of Document] Abstract

[Abstract]

[Object] A device for iontophoresis that can determine conduction states with a high level of accuracy, is provided.

[Means] This is a device to detect an electrical capacitance stored in transdermal or transmucosal. A voltage comparator 10B compares an output current signal 18 indicative of a reactive current flowing through a skin or a mucous with a threshold level SL pre-adjusted to a voltage value corresponding to a lower limit of the reactive current, thereby detecting the presence or absence of the reactive current. If the output current signal is higher than the threshold level, the voltage comparator 10B generates an output signal 11B of "H" to indicate to the controlling circuit that the conduction state is normal. If the output current signal is lower than the threshold level, the voltage comparator 10B generates an output signal 11B of "L" to indicate to the controlling circuit that the conduction state is abnormal.

[Selected figure] Fig.3